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Essence of harmony

The human body, with its multitude of complexities, requires harmonious interactions among all its constituents for the maintenance of homeostasis. Because every member of this intricate community has its own 'agenda', a peaceful and productive existence is not trivial. Fortunately, the body has several means for avoiding potential and detrimental conflicts between immune responses to self versus non-self. A fundamental strategy is ensuring that the immune cell repertoire is sufficiently devoid of those that could cause harm to self while maintaining a wide selection of those that are adept at taking appropriate action against foreign invaders and stressed cells. Another level of control is provided by the active regulation of immune responses through cellular interactions and soluble mediators. These checks and balances are the essence of harmony that maintains the status quo.

This issue of *Nature Immunology* examines how such harmony may be achieved by a subset of T lymphocytes called regulatory T cells (T_{reg} cells). The focus includes four review articles and a perspective that discuss the present understanding of the biology and function of these cells. Our focus website (www.nature.com/ni/focus/regulatory_tcells) offers access to all five articles, a selection of 'classic' papers considered by the community to have shaped the field, links to selected papers published by the Nature Publishing Group that pertain to these cells, and updated highlights of new research. All the content will be freely available to registered users in the month of April. We also acknowledge the support of Fujisawa Pharmaceuticals (now Astellas Pharma).

T_{reg} cells' is commonly used to describe a population of specialized T cells that express CD4 and CD25. Although all cells 'regulate' other cells in some way, T_{reg} cells are exceptional because their main role seems to be suppression of the function of other cells, hence they are also called 'suppressor cells'. Whether T_{reg} cells are unique may be supported by their ontogeny. Various data suggest T_{reg} cells represent a separate lineage of T cell education, a premise advocated by Fontenot and Rudensky in their discussion of T_{reg} cell development. Distinctively, the thymic development of T_{reg} cells straddles a 'window' of relatively high T cell receptor avidity for their selecting molecules without succumbing to deletion. As discussed by Fontenot and Rudensky as well as Sakaguchi, a further defining characteristic of T_{reg} cells is their expression of the transcription factor Foxp3, which supports the hypothesis for their special development. Despite recent advances, the precise requirements for the physiological development of T_{reg} cells, such as the necessary milieu, remain enigmatic. Understanding this is important for the generation of T_{reg} cells, both *in vivo* and *in vitro*, which could have enormous therapeutic potential, as discussed below.

Central to the understanding of T_{reg} cells is their mechanism of action. Although this is an area of intense research, the ground rules are far from definitive. Nevertheless, accumulated pieces of the puzzle,

as reviewed by von Boehmer, suggest important emerging themes. There are several modes of suppression by T_{reg} cells, ranging from the cytokines IL-10 and TGF- β to cell-cell contact via the inhibitory molecule CTLA-4. However, it is important to distinguish *in vitro* versus *in vivo* data, because they seem to diverge. Also, appreciation of *in vivo* suppression requires careful consideration of the location of T_{reg} and effector cell interaction.

Why the preoccupation with the biology of T_{reg} cells? The answer lies in their far-reaching effect on our health. T_{reg} cells may influence the outcome of infection, autoimmunity, transplantation, cancer and even allergy. However, the T_{reg} cell is very much a 'double-edged sword', creating a 'yin' for every 'yang' and vice versa, leading to an outcome that is context dependent. For example, Belkaid and Rouse discuss the detrimental effect of T_{reg} cells on immunity against infectious agents. Because T_{reg} cells can dampen immune responses, they may hamper effective control of viruses and bacteria. Experimental deletion of T_{reg} cells can lead to more efficient checking of pathogens. However, T_{reg} cells also dampen inflammation during infection, which is beneficial to the host. In addition, memory responses against particular pathogens such as leishmania may require some persistence, which necessitates the dampening of anti-leishmania immunity by T_{reg} cells.

Conceptually similar to their effect on immunity against pathogens, T_{reg} cells can also impede effective immunosurveillance of tumors. Thus, depletion of T_{reg} cells may lead to tumor rejection, but it may concurrently lead to autoimmunity. Sakaguchi highlights this classic example of delicate balance in his review. The involvement of T_{reg} cells in autoimmunity is clear, supported by genetic evidence whereby mutation of *Foxp3* leads to multiorgan autoimmune diseases both in mice and humans. Targeting of T_{reg} cells holds much promise for the treatment of these diseases, including the suppression of graft-versus-host diseases, which is now in clinical trials. However, greater understanding of T_{reg} cell biology is imperative, in particular the identification of a unique surface marker to facilitate their detection.

The quest to understand T_{reg} cells is now moving ahead full steam. In the throng of accumulating data, Schwartz provides a perspective on the present understanding of T_{reg} cells and how they relate to self-tolerance, their development and function, and their *raison d'être*. The existence of T_{reg} cells with such profound effect on myriad conditions underscores the complexity of the immune system and the need for multiple layers of oversight. This control system is not a static barrier but instead is a process of dynamic interaction with its microenvironment. The ultimate aim is to achieve the balance and harmony required for the well-being of the body, either naturally or through artificial intervention. Present wisdom suggests that T_{reg} cells are at the center of this equilibrium.